# *Development of cannabidiol as a treatment for severe childhood epilepsies*



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REVIEW ARTICLE

# Development of cannabidiol as a treatment for severe childhood epilepsies

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In recent years, there has been a growing appreciation by regulatory authorities that cannabis-based medicines can play a useful role in disease therapy. Although often conflagrated by proponents of recreational use, the legislative rescheduling of cannabis-derived compounds, such as cannabidiol (CBD), has been associated with the steady increase in the pursuit of use of medicinal cannabis. One key driver in this interest has been the scientific demonstration of efficacy and safety of CBD in randomised, placebo-controlled clinical trials in children and young adults with difficult-to-treat epilepsies, which has encouraged increasing numbers of human trials of CBD for other indications and in other populations. The introduction of CBD as the medicine Epidiolex in the United States (in 2018) and as Epidyolex in the European Union (in 2019) as the first cannabis-derived therapeutic for the treatment of seizures was underpinned by preclinical research performed at the University of Reading. This work was awarded the British Pharmacological Society Sir James Black Award for Contributions to Drug Discovery 2019 and is discussed in the following review article.

**KEYWORDS**
cannabidiol, Dravet syndrome, epilepsy

## 1 | INITIAL INTEREST IN CANNABIS COMPONENTS FOR TREATMENT OF EPILEPSIES

General interest in the potential therapeutic utility of non-tetrahydrocannabinol (THC) cannabinoids was pioneered by researchers such as Raphael Mechoulam at the Hebrew University of Jerusalem in Israel and Roger Pertwee, initially at Oxford University and then at Aberdeen University. In 2007, Gary Stephens and Ben Whalley had established an electrophysiology group at the University of Reading within the then new School of Pharmacy; they joined with Claire Williams from the School of Psychology and Clinical Language Sciences to investigate the role of plant-derived cannabinoids in different acute seizure models. Prior to joining the University of Reading, Ben Whalley, working with Andrew Constanti and Elizabeth Williamson at the London School of Pharmacy, had shown that standardised cannabis extracts lacking THC could inhibit muscarinic receptor agonist-induced epileptiform-like activity in ex vivo rat piriform cortical brain slices (Wilkinson et al., 2003). In parallel, Gary Stephens had an interest in the coupling of G protein-coupled receptors (GPCRs), such as cannabinoid $CB_1$ receptors, to downstream signalling pathways including voltage-gated calcium channels (Stephens, Canti, Page, & Dolphin, 1998; Stephens & Mochida, 2005;

**Abbreviations:** AED, anti-epileptic drug; CBD, cannabidiol; CBDV, cannabidivarin; CBG, cannabigerol; CBPM, cannabis-based products for medicinal use; DS, Dravet syndrome; FDA, Food and Drug Administration; GPCR, G protein-coupled receptor; GPR18, GPCR 18; GPR55, GPCR 55; LGS, Lennox–Gastaut syndrome; MES, maximal electroshock seizure; PTZ, pentylenetetrazole; RISE-SRS, reduced intensity status epilepticus-spontaneous recurrent seizures; THC, tetrahydrocannabinol; THCV, tetrahydrocannabivarin; TRPA1, transient receptor potential ankyrin 1; TRPV1, transient receptor potential vanilloid 1; TRPV2, transient receptor potential vanilloid 2; TSC, Tuberous Sclerosis Complex; VDAC1, voltage-dependent anion-selective channel protein 1; VGSC, voltage-gated sodium channel.

reviewed in Stephens, 2009). Claire Williams had complementary expertise in animal models of disease and, working with Tim Kirkham at Reading, had reported extensively on the effects of plant-derived phytocannabinoids, endocannabinoids, and exogenous cannabinoids in appetitive behavioural models. This work had demonstrated the role of $CB_1$ receptors in hyperphagia and highlighted the potential to target such receptors in obesity disorders (Williams & Kirkham, 1999; Williams, Rogers, & Kirkham, 1998; reviewed in Kirkham & Williams, 2004).

The common research interest of the team at Reading centred around epilepsy, a range of syndromes characterised by hyperexcitable neural networks in the brain, which clinically manifest as seizures and are associated with a clear unmet clinical need. Worldwide, there are around 65 M people with epilepsy, making it the most prevalent global neurological condition; however, around one third of patients with epilepsy do not respond to current anti-epileptic drugs (AEDs) and therefore live with uncontrolled seizures (Janmohamed, Brodie, & Kwan, 2019). Despite anecdotal reports of cannabis having therapeutic benefit in epilepsy, there had been little rigorous scientific research between 1970 and 2010 to support any clinical use, in particular with regard to preclinical efficacy, or safety and toxicity data. Our focus, **cannabidiol** (CBD), was isolated in 1963 (Mechoulam & Shvo, 1963) and first investigated functionally in the early 1970s (Paton & Pertwee, 1972). Amongst a few small-scale case studies, of particular interest was a study in Brazil suggesting that plant-derived CBD had potential utility in seizures (Cunha et al., 1980). By contrast, some reports had implicated THC as a pro-convulsant agent (as discussed in Rosenberg, Tsien, Whalley, & Devinsky, 2015). These findings were further set against the desire to find agents that did not promote the euphoria associated with recreational THC use.

The interest in use of non-psychoactive cannabinoids was supported by the introduction of Sativex (nabiximols, a 50:50 mixture of the two principal components of *Cannabis sativa*, THC and CBD) to relieve spasticity and pain associated with multiple sclerosis, representing the first cannabis-based medicine to be licensed in the United Kingdom. Thus, Stephens, Whalley, and Williams began collaborating with the intention of testing isolated cannabinoid extracts in seizure and epilepsy models. The makers of Sativex, GW Pharmaceuticals, initially partnering with Otsuka Pharmaceuticals, Japan, provided funding in 2007 to conduct preclinical research to assess the therapeutic potential of isolated phytocannabinoids in in vivo models of chemically induced seizures and associated in vitro studies to investigate modes and mechanisms of action. Individual phytocannabinoids, including CBD, were investigated as botanical drug substances.

Initial work using the $Mg^{2+}$-free and the 4-aminopyridine models of epileptiform activity in ex vivo rat hippocampal brain slices demonstrated clear CBD effects on local field potential burst amplitude, duration, and frequency in different cornus ammonis and dentate gyrus regions (Jones et al., 2010). Complementary work investigated the effects of CBD, applied via the intraperitoneal route, in a range of rat models of acute seizure induced by chemicals including pentylenetetrazole (PTZ) (to model generalised seizures) (Jones et al., 2010), pilocarpine (temporal lobe seizures), and penicillin (partial seizures) (Jones et al., 2012). Our initial in vivo work identified CBD as a major phytocannabinoid with the greatest anticonvulsant potential across all of the acute seizure models tested (Figure 1). It was similarly shown that intraperitoneal CBD was anticonvulsant in rat and mouse maximal electroshock seizure (MES) models, and in 6-Hz psychomotor and corneal kindling models, and that intravenous CBD was also effective in reduced seizure severity in the pilocarpine model (Patra et al., 2019; Figure 1). The latter study also showed that chronic administration of CBD oral solutions attenuated seizure burden and motor co-morbidities in the rat reduced intensity status epilepticus-spontaneous recurrent seizures (RISE-SRS) model of temporal lobe epilepsy (TLE) (Patra et al., 2019), the RISE-SRS model being developed between researchers at University of Reading and Gavin Woodhall's group at Aston University (Modebadze et al., 2016). From a pharmacological viewpoint, CBD was shown to possess only low, non-relevant binding affinity at $CB_1$ receptors (Jones et al., 2010); this work was in line with studies by other groups (as reviewed by Pertwee, 2008). These data also supported earlier work in the MES model in mice by Lisa Wallace and co-workers, who demonstrated that CBD had an anticonvulsant action, independent of effects on $CB_1$ receptors (Wallace, Wiley, Martin, & DeLorenzo, 2001). Following the investigation of CBD in human genetic paediatric epilepsies (described more fully below), we extended our studies to the effects of CBD in corresponding mouse models. In particular, we investigated models of Dravet syndrome (DS), a genetic disease due to a voltage-gated sodium channel (VGSC) *SCN1A* gene mutation. It was shown that chronic CBD (100 mg·kg$^{-1}$ injected subcutaneously twice daily) treatment was able to increase survival in *Scn1a*$^{-/-}$ mice and prevent premature mortality

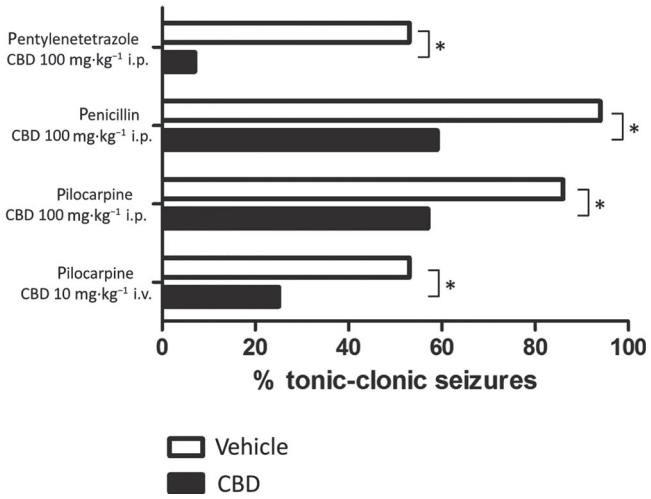


**FIGURE 1** CBD reduces seizure severity in different rat models of chemically induced acute seizure. Intraperitoneal CBD (100 mg·kg$^{-1}$) caused a significant reduction in seizure severity induced by pentylenetetrazole (80 mg·kg$^{-1}$ i.p., $n$ = 15; Jones et al., 2010), penicillin 525 IU intracerebroventricular infusion ($n$ = 17–18; Jones et al., 2012), or pilocarpine (380 mg·kg$^{-1}$ i.p., $n$ = 15; Jones et al., 2010). Intravenous CBD (10 mg·kg$^{-1}$) caused a significant reduction in seizure severity induced by pilocarpine (380 mg·kg$^{-1}$ i.v., $n$ = 12–15; Patra et al., 2019). *$P$ < 0.05, nonparametric binomial test

and improve associated co-morbidities in *Scn1a*$^{+/-}$ mice (Patra et al., 2020). Such preclinical work provided a strong association with the clinical data that had emerged following our initial work.

We have also investigated the effects of other phytocannabinoids. These compounds included the THC homologue **tetrahydrocannabivarin** (THCV), cannabigerol (CBG), and the CBD homologue cannabidivarin (CBDV). We initially showed that THCV had actions analogous to $CB_1$ receptor antagonists on inhibitory neurotransmission at interneuron-Purkinje cell synapses (Ma, Weston, Whalley, & Stephens, 2008). THCV was also shown to act as a $CB_1$ receptor antagonist in ligand binding and GTPγS binding assays (Dennis, Whalley, & Stephens, 2008; Hill et al., 2010). Interestingly, THCV reduced epileptiform activity induced by $Mg^{2+}$-free media in adult rat piriform cortical brain slices and demonstrated anticonvulsant effects against PTZ-induced generalised seizures in adult rats (Hill et al., 2010). The potential clinical utility of $CB_1$ receptor antagonists was however challenged by the high-profile withdrawal of the prototypic agent rimonabant. CBG was also shown to lack anticonvulsant effects in the PTZ model of generalised seizures (Hill et al., 2014). More prominently, we also demonstrated that CBDV possessed useful anticonvulsant effects in in vitro and in vivo seizure models (Amada, Yamasaki, Williams, & Whalley, 2013; Hill, Williams, Whalley, & Stephens, 2012). The former study further detailed the suppressive effects of CBDV on expression of specific epilepsy-related genes. We further demonstrated that the anticonvulsant effects of CBDV-rich cannabis extracts occurred independently of actions at $CB_1$ receptors (Hill et al., 2013). There are ongoing investigations into the potential clinical utility of CBDV in epilepsy; however, overall preclinical data in in vivo seizure models generated at the University of Reading strongly suggested CBD as a prominent cannabinoid which had clear potential to address the unmet clinical need associated with different forms of epilepsy.

## 2 | THE HUMAN EXPERIENCE

In parallel with efforts within the scientific research community, families of children with difficult-to-treat childhood epilepsies were beginning to connect with cannabis growers who were developing previously 'forgotten' high-CBD cannabis strains. The realisation that such strains may possess anti-seizure effects began to emerge via social and mainstream media. A notable example was the story of Charlotte Figi, which was captured in a memorable 2013 CNN documentary. At that time, Charlotte was a 5-year-old American girl who suffered dozens of seizures a day due to intractable DS, a disease associated with average life expectancy of just 8 years. Local producers of cannabis oil in Colorado developed a specialised high CBD/low THC product, later dubbed "Charlotte's Web," which was able to cause a remarkable reduction in Charlotte's seizure rate (Maa & Figi, 2014). Against a backdrop of Charlotte being a twin to a healthy sister, together with her father being in the US military, the human-interest documentary helped propel potential use of 'medical marijuana' into the public's consciousness. Other growers began to develop high CBD/low THC strains, and several families began to seek access to such strains, some via knowledge of the publications from University of Reading. In particular, the mother of Sam Vogelstein (a child with intractable childhood epilepsy who became Epidiolex patient #1) contacted GW Pharmaceuticals, citing the work of Jones et al. (2010), to request access to CBD. The treatment reportedly had significant efficacy—after 3 days of treatment, Sam was down from dozens of seizures per day to around one seizure per day. This led to the family being permitted by the Food and Drug Administration (FDA) to use CBD under a compassionate use program in California; the success of this program led to the pursuit of wider trials across more epilepsy centres. Thus, one of the foremost US epilepsy clinicians, Orrin Devinsky, Professor of Neurology at NYU Langone School of Medicine, oversaw moves towards the first randomised, controlled human clinical trials of CBD in patients with DS and another devastating paediatric epilepsy, Lennox–Gastaut syndrome (LGS). DS and LGS represent two of the most difficult to treat genetic childhood epilepsy syndromes; as patients with these syndromes have severely reduced lifespans and are commonly resistant to traditional AEDs, they represented a significant unmet need for new therapeutic options. These trials were further facilitated by the FDA decision in 2013 to grant CBD an Orphan Drug designation (i.e., special status to a drug with clear potential treat a rare disease, as defined in the United States as a condition that affects fewer than 200,000 people). Although classified as "rare" orphan diseases, figures from National Organization for Rare Diseases can be used to estimate that there are around 45,000–70,000 patients with DS and LGS in the United States. Such people with epilepsy present with multiple seizure types, commonly resistant to traditional AEDs, as well as developmental delay and numerous co-morbidities.

From 2014, open-label trials in patients with treatment-resistant epilepsy, including DS and LGS, were initiated. Such trials first reported an encouraging 36.5% median reduction in monthly motor seizures (Devinsky et al., 2016). Following successful Phase 2 trials (Devinsky et al., 2017; Devinsky, Patel, Thiele, & GWPCARE1 Part A Study Group, 2018), the first pivotal positive Phase 3 study results for CBD in the treatment of DS and LGS were announced. Each of these clinical studies recruited patients typically with a history of using at least two previous AEDs and displaying at least two uncontrolled seizures weekly during a 4-week pretreatment baseline. Across the studies, treatment groups displayed a significant ~20 percentage point decrease in seizures compared to placebo. Based on these positive human trials, the FDA approved Epidiolex as the first prescription plant extract cannabinoid medicine in the United States and as the first in a new class of anti-epileptic medications for the treatment of pharmacoresistant seizures in children and young adults with DS and LGS. Overall, the GWPCARE1 and GWPCARE2 trials demonstrated that an oral suspension of CBD at 10 or 20 $mg \cdot kg^{-1} \cdot day^{-1}$ two times a day had an acceptable safety profile and that individuals with treatment-resistant DS achieved a sustained, clinically meaningful reduction in monthly convulsive seizures compared with a placebo (Devinsky et al., 2017; Devinsky, Patel, Thiele, et al., 2018; Miller et al., 2020). Similarly, Phase 3 trials

for oral CBD in LGS (GWPCARE3 and GWPCARE 4) were also positive (Devinsky, Patel, Cross, et al., 2018; Thiele et al., 2018). Thus, four major trials were carried out, recruiting a total of 550 (DS, 154; LGS, 396) patients who had previously been unable to control their seizures despite AED polytherapy (see Morano et al., 2020). An open-label extension trial, GWPCARE5, with 630 subjects (DS, 264; LGS, 366) further supported oral CBD safety and persistence efficacy in DS and LGS patients (Devinsky et al., 2019; Thiele, Bebin, et al., 2019). Prior to Epidiolex being available for prescription, it has been estimated that over 2,000 patients had already been treated through GW's compassionate use program and open-label extension. Epidiolex became available for prescription in the United States in November 2018. The Drug Enforcement Agency reclassified CBD (containing no more than 0.1% [w/w] residual THC) to Schedule V, indicating proven medical use and low potential for abuse. Similar European Medicine Authority approval for CBD followed in 2019, under the brand name Epidyolex. In the United Kingdom, the medicine became fully available on the NHS in January 2020. Drug scheduling of cannabis in the United Kingdom has been under regular review, and in November 2018, "cannabis-based products for medicinal use (CBPMs)" were reclassified from Schedule 1 controlled drugs (compounds of no medical value) into Schedule 2 of the Misuse of Drugs Regulations 2001. Most recently, Epidyolex was reclassified as a Schedule 5 drug in the United Kingdom.

During approval, FDA Commissioner Scott Gottlieb stated in a press release: "This approval serves as a reminder that advancing sound development programs that properly evaluate active ingredients contained in marijuana can lead to important medical therapies. And, the FDA is committed to this kind of careful scientific research and drug development."

## 3 | CBD MECHANISM OF ACTION

A definitive pharmacological target for CBD in epilepsy (and elsewhere) remains elusive, with various reports of pharmacologically relevant affinity at several molecular targets (Gray & Whalley, 2020; Senn, Cannazza, & Biagini, 2020). The best recognised targets include transient receptor potential vanilloid channels and **GPCR 18** (GPR18) and **GPR55** receptors (Alexander et al., 2019). Work at the University of Reading has contributed to descriptions of CBD activation, and subsequent desensitisation, of **transient receptor potential vanilloid 1** (TRPV1), **TRPV2**, and **transient receptor potential ankyrin 1** (TRPA1) (Iannotti et al., 2014). We have also shown that CBD blocks the activation of GPR55 receptors by the endogenous lipid agonist lysophosphatidylinositol in ex vivo brain slices taken from rats displaying spontaneous epileptiform activity (Rosenberg et al., 2018).

Pharmacological blockage/antagonism and/or transgenic technology is good evidence to define mechanism of action. One recent study demonstrates that CBD's anticonvulsant properties were attenuated in TRPV1 knockout mice (Gray, Stott, Jones, Di Marzo, & Whalley, 2020). CBD also acts as allosteric modulator of $5HT_{1A}$; however, one specific study has ruled out $5HT_{1A}$ as a CBD target in seizure control (Pelz, Schoolcraft, Larson, Spring, & Lopez, 2017). CBD was also shown to act as a blocker of VGSCs (Hill et al., 2014), which represents a potential mode of anticonvulsive action in epilepsy. However, another phytocannabinoid, CBG, was shown to share blockade of VGSCs but, unlike CBD, had no clear effect on PTZ-induced seizures in rats (Hill et al., 2014). CBD has also been shown to retain anti-seizure effects and improve social deficits and survival in a mouse model of DS (Kaplan, Stella, Catterall, & Westenbroek, 2017; Patra et al., 2020), itself a syndrome associated with a loss-of-function mutation to $Na_V1.1$ VGSCs. Moreover, nanomolar CBD was effective in regulating neuronal excitability without effects on VGSCs in a human-induced pluripotent stem cell-based model of DS (Sun & Dolmetsch, 2018). Such data suggest that VGSCs were not the primary CBD target in epilepsy; these findings are significant as current AEDs which act as VGSC blockers are known to exacerbate DS.

As described above, CBD has only very low affinity at $CB_1$ receptors; correspondingly, CBD lacks any appreciably coupling to G protein turnover (Jones et al., 2010). There are however reports that CBD can act as a negative allosteric modulator at $CB_1$ receptors (Laprairie, Bagher, Kelly, & Denovan-Wright, 2015; Straiker, Dvorakova, Zimmowitch, & Mackie, 2018) and also as a partial agonist at $CB_2$ receptors (Tham et al., 2019). Of further mechanistic interest is our recent study which was consistent with CBD ameliorating the pro-convulsant effect of long-term THC treatment in rats (Whalley et al., 2018). In this study, we also described a potential mechanism whereby CBD reduced THC-mediated $CB_1$ receptor activation in a species-specific way (Figure 2); such CBD actions may reflect a functional reduction in seizures, for example, via negative allosteric modulation of $CB_1$ receptors.

Several other potential molecular targets of CBD, including classical receptors, ion channels, transporters, and enzymes, have been proposed (reviewed by us in Hill et al., 2012; Ibeas Bih et al., 2015; Turner, Williams, Iversen, & Whalley, 2017). Most prominent amongst these are alternative receptor targets including $5HT_{1A}$, adenosine receptor subtypes, and PPARγ nuclear receptors; additional ion channel targets including $Ca_V3$ voltage-gated calcium channels and mitochondrial voltage-dependent anion-selective channel protein 1 (VDAC1); adenosine transporters; and, potentially, enzymes involved in the endocannabinoid system, such as fatty acid amide hydrolase. One common CBD effect may be the modulation of downstream levels of calcium as a second messenger (see Ibeas Bih et al., 2015). In this regard, CBD has been proposed to regulate mitochondrial control (potentially via VDAC1) of intracellular calcium levels in hippocampal neurons and to restore homeostasis in pathological situations (Ryan, Drysdale, Lafourcade, Pertwee, & Platt, 2009); such function may contribute to CBD effects in epilepsy. More recently, we and co-workers have shown that CBD can act on a glycine cleavage system component to inhibit synthesis of the essential amino acid methionine, including in heterozygous $Scn1a^{+/-}$ mice in the DS model (Perry et al., 2020). This work introduces one-carbon signalling as a further potential target for CBD action.

A potential confounder in some studies is the use of high (∼ >10 μM) CBD concentrations. As discussed by us previously, the

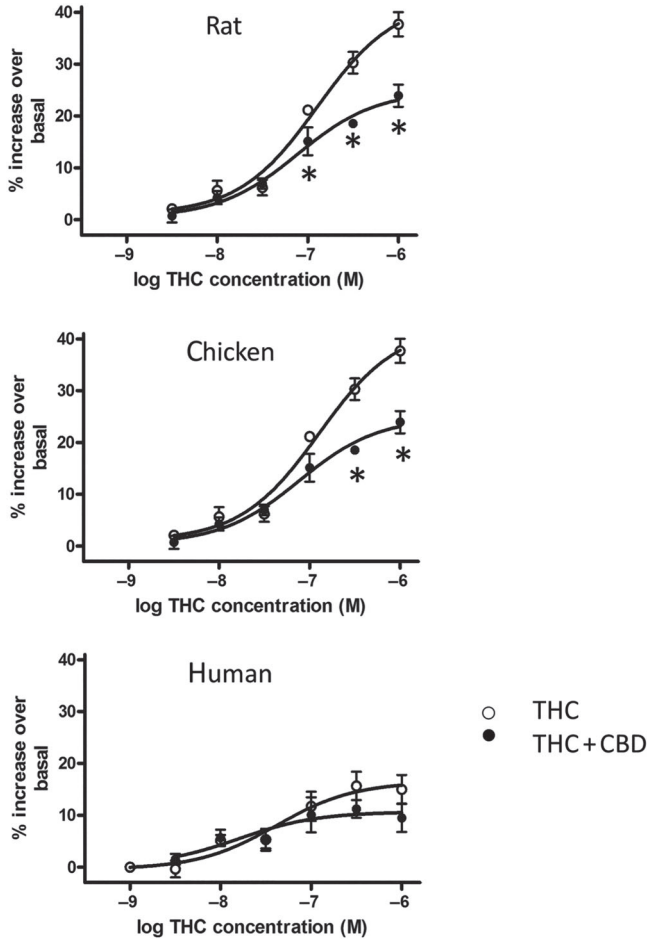


**FIGURE 2** CBD affects THC-stimulated $^{35}$S-GTPγS turnover in cerebellar tissue in a species-specific manner. CBD (applied at a THC: CBD 1.08:1 ratio) attenuated THC-stimulated G protein turnover in rat and chicken, but not human, tissue. Note that in human tissue, THC-stimulated G protein turnover was of generally lower magnitude. *$P$ < 0.05, ANOVA followed by a Tukey's post hoc test on raw data from three separate experiments in triplicate, preparations from multiple brains (data derived from Whalley et al., 2018)

lipophilic nature of CBD means that results based on higher micromolar concentrations of CBD are likely influenced by insertion of CBD into the plasma membrane (Ibeas Bih et al., 2015). In practice, the poor bioavailability of CBD in vivo (see below) may limit these effects. However, the general lipophilic profile of cannabinoids, including CBD, also means that they have potential to accumulate in fatty tissue and be released over time. In general, more credence is typically placed on CBD effects that occur at low/sub-micromolar concentrations. Overall, CBD may exhibit a relevant "polypharmacology" profile; there are also consistent reports of anti-oxidant and anti-inflammatory properties of CBD which have potential to contribute to anti-epileptic (and other) effects.

Finally here, the lack of a well-defined molecular target can lead to speculation about the potential role of metabolites. In humans, CBD is metabolised mainly into 7-OH-CBD and the major 7-COOH-CBD metabolite. However, work on effects of CBD metabolites is, as yet, still in its infancy.

## 4 | CLINICAL/FUTURE PERSPECTIVES

Over the last few years, there has been an explosion in interest in the use of CBD-containing foods and supplements, supported by widespread availability of numerous different CBD preparations on the High Street and of further unregulated access via the internet. There have been recent warnings about levels of such consumption from the UK Food Standards Agency and efforts to curtail many unsubstantiated claims of therapeutic benefit. The latter will, of course, require controlled human trials which investigate appropriate formulations of standardised product, delivered at an efficacious dose. The original case of Charlotte Figi described above has several recent parallels in the United Kingdom. The publicity around cases of uncontrolled childhood epilepsies, such as those of Billy Caldwell and Alfie Dingley, were key in the reclassification and increased availability of CBPMs, including those with a CBD component. These moves were no doubt also fuelled by the approval of Epidiolex as a scientifically tested medicine.

From a clinical viewpoint, there are challenges to effective delivery of CBD. Animal studies suggest that CBD oral bioavailability is low (<20%) (Mechoulam, Parker, & Gallily, 2002), with CBD being subject to extensive first-pass metabolism (Huestis, 2007); however, wide-ranging human data for CBD bioavailability are currently lacking (Millar et al., 2019). CBD is also associated with low water solubility and variability in pharmacokinetic profiles (Millar, Maguire, Yates, & O'Sullivan, 2020). Therefore, further work is needed to establish therapeutic dosing and most effective route of administration. Clinically, Epidiolex is given as an oral solution; in addition, the CBD-containing medicine Sativex is administered sublingually to avoid first-pass metabolism. CBD bioavailability may be improved by intranasal delivery (e.g., of vaporised drug) or even by transdermal delivery (Paudel, Hammell, Agu, Valiveti, & Stinchcomb, 2010). However, of interest for anticonvulsant effects is that CNS levels of CBD were found to be higher via the oral, compared to the inhaled, route; moreover, such exposure correlated with increased behavioural effects (Hložek et al., 2017).

There is a well-described "entourage effect," originally posited for the endocannabinoid system by Ben-Shabat et al. (1998), whereby cannabinoid effects are synergically increased by associated components. Such effects have also been ascribed to CBD and to Epidiolex, which represents a 98% CBD plant extract; however, future controlled human trials will be required to more fully define this effect. Some evidence in support of CBD synergism comes from a recent meta-analysis of observational clinical studies that concluded patients required ~4-fold less CBD dose in enriched plant extracts versus purified drug and that adverse effects were also reduced in extracts (Pamplona, da Silva, & Coan, 2018). An additional challenge is to define the nature and contribution of the highly numerous additional components in cannabis.

Epilepsy is a condition prone to a "honeymoon" effect, that is, a reduction of initial drug efficacy with prolonged use, often associated with development of tolerance to AEDs (Avanzini, 2006; Dale et al., 2019). It remains unclear if people with epilepsy will develop

similar tolerance to CBD. At present, there is no published evidence for CBD tolerance in other conditions; however, a recent open-label study reported that around one third of paediatric and adults with different treatment resistance epilepsies showed some tolerance to CBD-enriched oil in terms of reduced control of mean monthly seizure frequency (although concomitant medication was maintained) (Uliel-Sibony, Hausman-Kedem, Fattal-Valevski, & Kramer, 2020). Follow-up studies to further investigate CBD tolerance in epilepsy, and its relevance in comparison to AEDs, are thus warranted.

Epidiolex may be given as a monotherapy in the United States in uncontrolled DS and LGS and Epidyolex as an adjunct to standard anti-epileptic therapies in the European Union. CBD is generally considered a safe drug (Taylor, Gidal, Blakey, Tayo, & Morrison, 2018), in particular, in comparison to standard AEDs (Bergamaschi, Queiroz, Zuardi, & Crippa, 2011; Iffland & Grotenhermen, 2017). Original studies reported that CBD caused some adverse effects, including tiredness, diarrhoea, and changes of appetite/weight (Huestis et al., 2019); however, many such adverse effects occur at doses higher than those used for seizure control. A major CBD effect is inhibition of hepatic drug metabolism leading to recognised, significant increases in the levels of several co-administered AEDs (Gaston, Bebin, Cutter, Liu, & Szaflarski, 2017). A common standard AED used in conjunction with Epidiolex is clobazam. One report (in a preclinical model) has proposed that an interaction between CBD and clobazam may underlie improved anti-epileptic profiles (Anderson et al., 2019), potentially via CBD inhibition of CYP2C19, which metabolises clobazam. However, recent open-label studies have shown that such interactions appear to have no effect on seizure frequency and severity outcomes in the patient population (Gaston et al., 2019; Savage et al., 2019). Isobolographic studies (which are gold standard for pharmacological interactions) for CBD (and 7-OH-CBD) and clobazam (and the major metabolite *N*-desmethylclobazam) indicated a synergistic action in the MES mouse model of acute generalised seizures that occurred independently of pharmacokinetic interaction (Rana, 2019). A recent meta-analysis further suggests that CBD has anti-seizure efficacy independent of clobazam administration (Lattanzi et al., 2020).

With the recent approval of Epidiolex, several other disease states are the subject of intense investigation with regard to CBD use, with many now progressing to human trials. Recent reviews have outlined clinical work on CBD in, amongst others, Parkinson's disease and psychosis, society anxiety disorder, Rett syndrome, schizophrenia, cognitive dysfunction, and ulcerative colitis and Crohn's disease, as well as the potential for CBD to counteract recreational use of cannabis and dependence on opioids (Millar et al., 2019; Pauli, Conroy, Van Den Heuval, & Park, 2020). In particular, positive results from Phase III trials showing that CBD reduced seizures associated with Tuberous Sclerosis Complex (TSC) were reported in the GWPCARE6 study (Thiele, Marsh, et al., 2019); this work was also supported by our mechanistic work on CBD effects in a zebrafish model of TSC (Serra et al., 2019). CBD is also being widely investigated in different forms of cancer (Hinz & Ramer, 2019). This activity strongly suggests that CBD therapeutic use will likely soon extend to other conditions.

Thus, preclinical developmental work on CBD at the University of Reading leading to the introduction of Epidiolex for the treatment of severe childhood epilepsies has been recognised by the British Pharmacological Society, which has awarded Stephens, Whalley, and Williams the 2019 Sir James Black Award for Contributions to Drug Discovery. Much of this initial and ongoing work has been published in the *British Journal of Pharmacology*, including in different themed issues on cannabinoids, and has been presented at European Workshops on Cannabinoid Research organised by the BPS and several annual BPS Pharmacology meetings. The commitment of the BPS to this area of preclinical work has helped push CBD to the clinic for paediatric epilepsies; it is highly likely that additional areas of therapeutic utility will arise in the next few years for CBD and perhaps other plant-derived cannabinoids.

## 4.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander et al., 2019).

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### AUTHOR CONTRIBUTIONS

C.W. and G.S. contributed to preclinical work discussed in this review and wrote the manuscript.

### CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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